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Cardiovascular Outcomes in the AFFIRM Trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management)

An Assessment of Individual Antiarrhythmic Drug Therapies Compared With Rate Control With Propensity Score-Matched Analyses

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Objectives The impact of individual antiarrhythmic drugs (AADs) on mortality and hospital stay in atrial fibrillation (AF) was evaluated.

Background Cardiovascular (CV) outcomes in AF patients receiving pharmacologic rhythm control therapy have not been compared with rate control therapy on the basis of AAD selection.

Methods We compared CV outcomes in the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) trial in subgroups defined by the initial AAD selected with propensity score matched subgroups from the rate arm (Rate).

Results Seven hundred twenty-nine amiodarone patients, 606 sotalol patients, and 268 Class 1C patients were matched. The composite outcome of mortality or cardiovascular hospital stays (CVH) showed better outcomes with Rate compared with amiodarone (hazard ratio [HR]: 1.18, 95% confidence interval [CI]: 1.03 to 1.36, $p = 0.02$), sotalol (HR: 1.32, 95% CI: 1.13 to 1.54, $p < 0.001$), and Class 1C (HR: 1.22, 95% CI: 0.97 to 1.56, $p = 0.10$). There was a nonsignificant increase in mortality with amiodarone (HR: 1.20, 95% CI: 0.94 to 1.53, $p = 0.15$) with the risk of non-CV death being significantly higher with amiodarone versus Rate (HR: 1.11, 95% CI: 1.01 to 1.24, $p = 0.04$). First CVH event rates at 3 years were 47% for amiodarone, 50% for sotalol, and 44% for Class 1C versus 40%, 40%, and 36%, respectively, for Rate (amiodarone HR: 1.20, 95% CI: 1.03 to 1.40, $p = 0.02$, sotalol HR: 1.364, 95% CI: 1.16 to 1.611, $p < 0.001$, Class 1C HR: 1.24, 95% CI: 0.96 to 1.60, $p = 0.09$). Time to CVH with intensive care unit stay or death was shorter with amiodarone (HR: 1.22, 95% CI: 1.02 to 1.46, $p = 0.03$).

Conclusions In AFFIRM, composite mortality and CVH outcomes differed for Rate and AADs due to differences in CVH; CVH event rates during follow-up were high for all cohorts, but they were higher for all groups on AADs. Death, intensive care unit hospital stay, and non-CV death were more frequent with amiodarone. (Atrial Fibrillation Follow-Up Investigation of Rhythm Management; NCT00000556) (J Am Coll Cardiol 2011;58:1975–85) © 2011 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most prevalent tachyarrhythmia and is associated with increased mortality, stroke, and recurrent hospital stays (1,2). Health care resource con-

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Abbreviations and Acronyms

AAD = antiarrhythmic drug
AF = atrial fibrillation
CI = confidence interval
CV = cardiovascular
CVH = cardiovascular hospital stay(s)
HR = hazard ratio
ICU = intensive care unit
Rate = rate control strategy arm

sumption due to AF, primarily due to hospital stay, is among the highest for cardiovascular (CV) diagnoses, but the patterns of these hospital stays and their relationship to individual therapeutic choices in AF have not been evaluated (3). The AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) trial was conducted to examine 2 treatment strategies for AF, namely rate control or rhythm control (4,5). All-cause mortality, the primary outcome measure, showed a trend toward excess mortality in the rhythm control arm. The antiarrhythmic drugs (AADs) used in the rhythm arm have been cited as a potential cause of the excess mortality (6). Despite concerns with regard to their safety, most of the AADs used in the AFFIRM trial remain widely used in clinical practice.

The impact of individual AADs on mortality and hospital stay outcomes in the AFFIRM population in relation to rate control has not been available. In part, this was related to the intent of the AFFIRM investigators to test the treatment strategy hypothesis rather than individual drug therapies. In this report, we examined the impact on outcomes of the selection of amiodarone, sotalol, or a Class 1C antiarrhythmic agent (flecainide or propafenone) as the first AAD, compared with a rate strategy in the AFFIRM study. The AADs were selected for this analysis on the basis of current widespread clinical usage. To address the nonrandom nature of drug selection in the rhythm arm, we employed propensity score matching derived from 64 baseline patient characteristics deemed to affect antiarrhythmic selection. Propensity score matching has not been employed to assess individual drug outcomes in the AFFIRM trial (7). We compared mortality and hospital stay outcomes in patient subgroups defined by each type of AAD selected as first therapy with propensity score matched subgroups from the rate control arm.

Methods

Patient Selection in the AFFIRM Trial

The AFFIRM trial recruited consenting patients who had AF that was likely to be recurrent, warranted therapy, and had risk factor(s) for stroke. Patients were candidates for at least 2 drugs within each strategy and for anticoagulation (4).

Primary Objective of Analysis

Reassessment of clinical outcomes by initial AAD therapy. The primary objective was to reassess clinical outcomes in the AF population enrolled in the AFFIRM study by initial AAD therapy with a composite principal outcome and its individual components. The principal outcome was a composite of mortality or first cardiovascular hospital stay (CVH). Individual components (all-cause mortality and CVH) were also examined, as were subsets of both CVH and all-cause mortality (8). The AAD subgroups were compared with propensity score matched rate subgroups (Rate) and included: 1) initial amiodarone therapy (amiodarone cohort); 2) initial sotalol (sotalol cohort); and 3) initial Class 1C drug (flecainide or propafenone, Class 1C cohort).

Propensity score matched subgroups were selected from the rate control strategy arm (Rate) for each AAD cohort. The score was derived with 62 baseline patient characteristics from the AFFIRM database deemed a priori to potentially affect AAD selection. Two additional characteristics that were determined to be important to achieve balanced cohorts (left ventricular ejection fraction, and history of coronary artery disease) were added in a second step (Table 1).

Secondary Objectives

Relating outcomes to clinical and treatment factors. The severity of CVH was characterized by acuity of hospital stay on the basis of concomitant intensive care unit (ICU) stay, CV procedures, CV interventions, or emergency room visits. Outcomes in AAD subgroups were related to patient characteristics, underlying disease state, clinical events, and treatment strategy.

Study Outcomes and Definitions

The principal outcome for this analysis was a composite outcome: the first of death from any cause or a CVH. A CVH was defined as a hospital admission for CV reasons (per investigator) or for non-CV reasons but with a CV event occurring during the same follow-up interval. Exact dates were available for death but not for hospital admission or discharge. The midpoint of the previous follow-up visit and the follow-up visit when the hospital stay was reported were used to estimate event time for CVH. Investigators recorded total number of hospital days and total number of ICU days. Visits occurred at 2 months after randomization and every 4 months thereafter. Patients who did not experience CVH or death were censored at the last follow-up visit. For death alone, follow-up information from a vital status sweep (telephone contact with all subjects and national death index scan) at the end of the study was used to determine censoring date.

Statistical Methods and Analytical Techniques

Propensity score and establishment of matched cohorts. The goal of development of propensity score matched cohorts was to account for possible confounding variables that might be related to drug selection, because the patients were not assigned randomly to specific initial drug therapy in the AFFIRM trial.

Selection of covariates. Propensity score was calculated separately for each AAD subgroup (amiodarone, sotalol, or Class 1C). Four patients received more than 1 AAD and

Table 1 Covariates Used in Propensity Score Model

Age	Primary cardiac diagnosis
Sex	Coronary artery disease
Year of randomization	NYHA
Site	Current CCS angina class
FADS site	Failed any AAD
History of myocardial infarction	Number of AAD failures
History of pulmonary disease	Failed amiodarone
History of intracranial hemorrhage	Failed disopyramide
History of congestive heart failure, congestive heart failure on enrollment	Failed flecainide
History of cardiomyopathy	Failed moricizine
History of valvular heart disease	Failed procainamide
History of congenital heart disease	Failed propafenone
History of angina	Failed quinidine
History of diabetes	Failed sotalol
History of hepatic or renal disease	Failed other AAD
History of symptomatic brady/atrioventricular block	Previous other CV procedure
History of resuscitated cardiac arrest	Previous percutaneous coronary interventions
History of stroke/transient ischemic attack	Previous coronary artery bypass grafting
History of peripheral vascular disease	Previous thrombolytic therapy
History of systemic embolism	LV ejection fraction
History of hemorrhage or coagulopathy	Beta stimulant
History of thyroid disease/specific drugs—thyroid replacement	Theophylline
History of carotid disease	Diuretic
Symptoms constellations are	Beta-blockers
1. Chest pain	
2. Diaphoresis, fatigue, panic, dizziness, syncope	
3. Diuresis	
4. Dyspnea, edema, orthopnea, paroxysmal nocturnal dyspnea	
5. Fast heart rate, palpitations	
AF symptoms frequency	Diltiazem
First AF episode	Verapamil
Duration of qualifying AF episode(s)	BMI
Hospitalized for qualifying episode	SBP
Cardioverted for qualifying episode(s)	FADS patient
Current ventricular/max HR during AF >100 beats/min	Other cardiac neurologic interaction

List of covariates used in propensity score model. Please note that multiple imputation was used for body mass index (BMI) and systolic blood pressure (SBP).

AAD = antiarrhythmic drug; AF = atrial fibrillation; BMI = body mass index; CCS = Canadian Cardiovascular Society; CV = cardiovascular; FADS = first antiarrhythmic drug substudy; HR = heart rate; LV = left ventricular; max = maximum; NYHA = New York Heart Association functional class; SBP = systolic blood pressure.

were excluded. The propensity score model used data from AFFIRM patients randomized to rhythm control. Identical baseline explanatory variables were included in each model and were prospectively determined by consensus before data analysis (Table 1). This model included explanatory variables that might be considered by clinicians when selecting an AAD, including demographic data, clinical characteristics of patients, treating physicians (cardiologists or other), centers, and study design factors. Patients in the first AAD substudy had their first AAD randomly assigned, so participation in first AAD sub-study was included as a variable (9). A stepwise model reduction procedure was used to produce a parsimonious model for each propensity score equation. After initial cohort construction, imbalances in 2 additional variables, coronary artery disease and left ventricular ejection fraction, were identified; these items were added to the model in a second step.

Model building. Proc GLIMMIX in SAS (version 9.2, SAS Institute, Cary, North Carolina) was used for building the propensity-matched cohorts. Each model considered all explanatory variables in Table 1. Site was included as a fixed effect for this step. The functional form of response was assessed for continuous variables to determine whether transformation was necessary (10). Then, the model was run twice, with site as a fixed and then as a G-sided (generalized) random effect. These models were compared for evidence of extra binomial variability at the investigator site level. Risk score was calculated for each patient in the rate subgroup, and the VMATCH algorithm (Zentrum fur Bioinformatik, Hamburg, Germany) was used to construct the cohorts (7). Matching was 1:1 between each AAD cohort and the rate cohort.

Descriptive reporting. Once the propensity score matched cohorts were established, baseline demographic and clinical characteristics were tabulated to be consistent with the main

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AFFIRM publication (5). Tests for differences across matched cohorts were conducted (Fisher exact or chi-square for categorical variables, analysis of variance or Wilcoxon for continuous variables).

Principal Outcome

The principal outcome analyzed was a comparison of event time with the log-rank test on an intention-to-treat basis, similar to the primary AFFIRM analysis. Unadjusted Kaplan-Meier survival curves were examined for each propensity-score matched cohort pair. Proportional hazards models were used to obtain hazard ratios (HRs) and 95% confidence intervals (CIs) and to determine the effect in clinically important subgroups.

Sensitivity analyses. To determine the impact of treatment strategy-related hospital stays, (e.g., cardioversions) and further define acuity of CVH, we repeated the analysis with a composite of death and first hospital stay requiring ICU stay. To evaluate the propensity score methodology, a Cox proportional hazards model with a frailty term for site was used.

Results

Patient population. Seven hundred twenty-nine AF patients initially received amiodarone therapy, 606 received initial sotalol therapy, and 268 received either initial flecainide or propafenone. The clinical characteristics of these 3 AAD cohorts on the basis of initial drug therapy selection are shown in Table 2. The AAD cohorts were generally well-matched. Patients were usually elderly, predominantly male, and had recurrent AF associated with cardiac disease. The amiodarone cohort had a slight excess of men, compared with its matched Rate cohort (67.4% vs. 61.3%, respectively). More patients in the sotalol cohort had a history of angina, compared with Rate (11.1% vs. 6.9%).There were no other significant differences. The C statistic for the 3 propensity models were 0.814 for amiodarone, 0.837 for sotalol, and 0.837 for Class 1C subgroups.

Outcomes analysis. HRs and 95% CIs for the overall comparison (rhythm compared with rate) in the AFFIRM trial and individual AAD subgroups with the matched rate cohort are shown for the composite principal outcome of mortality and first CVH in Figure 1. All AAD cohorts had inferior principal outcomes, compared with Rate (HR for amiodarone: 1.18, 95% CI: 1.03 to 1.36, $p = 0.02$; HR for sotalol: 1.32, 95% CI: 1.13 to 1.54, $p < 0.001$; and HR for Class 1C: 1.22, 95% CI: 0.97 to 1.56, $p = 0.10$). In the smaller Class 1C cohort, this difference did not reach statistical significance. Figure 2 shows the individual components of the composite endpoint. Risk of CVH was increased for all 3 AAD cohorts (amiodarone HR: 1.20, 95% CI: 1.03 to 1.40, $p = 0.05$; sotalol HR: 1.36, 95% CI: 1.16 to 1.61, $p < 0.001$; and Class 1C HR: 1.24, 95% CI: 0.96 to 1.64, $p = 0.09$, compared with Rate). Ninety-one percent of amiodarone patients, 88% of sotalol patients, and 78% of Class 1C patients were receiving the initially selected drug at first CVH. There was no increased mortality risk for sotalol and Class 1C cohorts, but an increase in risk was observed for amiodarone (HR: 1.20, 95% CI: 0.94 to 1.53, $p = 0.15$), compared with Rate, which was not statistically significant. Time to first CVH was shorter for all AADs, compared with Rate. First CVH event rates at 3 years were 47% for amiodarone, 50% for sotalol, and 44% for Class 1C compared with 40%, 40%, and 36%, respectively, for the matched Rate cohorts. The CV mortality did not differ between Rate and any of the AAD cohorts ($p > 0.15$ for all comparisons). There was an increased risk of noncardiovascular mortality with amiodarone (HR: 1.11, 95% CI: 1.01 to 1.24, $p = 0.04$) but not with sotalol or Class 1C drugs, compared with Rate. However, deaths attributable to cancer or pulmonary causes were comparable across each cohort.

A composite of death or ICU hospital stays showed moderately increased risk with amiodarone (HR: 1.22, 95% CI: 1.02 to 1.46, $p = 0.03$) but not with sotalol or Class 1C agents (HR: 1.06, 95% CI: 0.87 to 1.30, $p = 0.56$, and HR: 1.07, 95% CI: 0.78 to 1.46, $p = 0.67$, respectively), compared with Rate (Fig. 3A). There was no difference in time to ICU hospital stays for sotalol and Class 1C, compared with Rate, but a nonsignificant increased risk was noted for amiodarone (HR: 1.18, 95% CI: 0.95 to 1.47, $p = 0.14$) (Fig. 3B). All-cause hospital stays were increased in amiodarone compared with Rate (HR: 1.19, 95% CI: 1.05 to 1.35, $p = 0.008$) and in sotalol compared with Rate (HR: 1.22, 95% CI: 1.06 to 1.41, $p = 0.005$). There was no increased risk of all-cause hospital stay with Class 1C compared with Rate.

Concomitant beta-blocker therapy did not alter outcomes for either sotalol or Class 1C cohorts for either mortality or CVH risk (CVH for sotalol HR: 1.09, 95% CI: 0.89 to 1.34, for death HR: 1.15, 95% CI: 0.81 to 1.63; CVH for Class 1C HR: 0.75, 95% CI: 0.60 to 1.03), for death HR: 0.65, 95% CI: 0.40 to 1.07). Amiodarone-Rate cohort patients who were concomitantly taking beta-blockers had an increased mortality risk (CVH risk for amiodarone HR: 1.06, 95% CI: 0.90 to 1.25, for death HR: 1.53, 95% CI: 1.16 to 2.02). There was no evidence of a treatment–digoxin interaction for the principal outcome. Time-dependent digoxin use was significantly associated with CVH in the amiodarone-Rate cohorts (HR: 1.43, 95% CI: 1.21 to 1.68) and in the Class 1C-Rate cohorts (HR: 1.36, 95% CI: 1.04 to 1.77) but not in the sotalol-Rate cohorts (HR: 1.15, 95% CI: 0.96 to 1.37). After adjusting for time-dependent digoxin use, AADs still increased the risk of CVH (HR for amiodarone: 1.34, 95% CI: 1.13 to 1.57, HR for sotalol: 1.40, 95% CI: 1.17 to 1.67, compared with matched rate patients; HR for Class 1C: 1.34, 95% CI: 1.03 to 1.75, compared with the respective AAD rate-matched patients). The increased risk of CVH or death was consistent across clinically important subgroups including coronary disease, female sex, and age for amiodarone and sotalol patients, presence of thyroid disease only in amiodarone

Table 2 Baseline Patient Characteristics for Entire Rate Cohort in AFFIRM

	Overall Rate (Original) (n = 2,027)	Rate (PS Matched) (n = 729)	Amiodarone (PS Matched) (n = 729)	p Value	Rate (PS Matched) (n = 606)	Sotalol (PS Matched) (n = 606)	p Value	Rate (PS Matched) (n = 268)	Class 1C (PS Matched) (n = 268)	p Value
Age, yrs	69.8 ± 8.91	69.7 ± 8.79	70.3 ± 9.2	0.21	70.5 ± 8.4	69.6 ± 8.8	0.06	68.6 ± 9.3	68.6 ± 8.9	0.94
Female	823 (40.6%)	282 (38.7%)	238 (32.6%)	0.02	234 (38.6%)	227 (37.5%)	0.68	144 (53.7%)	140 (52.2%)	0.73
Ethnic minority group	241 (11.9%)	98 (13.4%)	78 (10.7%)	0.11	70 (11.6%)	57 (9.4%)	0.22	23 (8.6%)	24 (9.0%)	0.88
Predominant cardiac diagnosis				0.92			0.74			0.66
Coronary artery disease (MI, angina, and so on)	497 (24.5%)	228 (31.3%)	247 (33.9%)		165 (27.2%)	158 (26.1%)		28 (10.4%)	31 (11.6%)	
Dilated cardiomyopathy	99 (4.9%)	53 (7.3%)	52 (7.1%)		22 (3.6%)	20 (3.3%)		5 (1.9%)	5 (1.9%)	
Hypertension	1,045 (51.6%)	351 (48.1%)	342 (46.9%)		291 (48.0%)	315 (52.0%)		154 (57.5%)	156 (58.2%)	
Valvular heart disease	98 (4.8%)	30 (4.1%)	28 (3.8%)		34 (5.6%)	34 (5.6%)		9 (3.4%)	15 (5.6%)	
Other	23 (1.1%)	9 (1.2%)	7 (1.0%)		13 (2.1%)	9 (1.5%)		3 (1.1%)	1 (0.4%)	
No apparent heart disease	265 (13.1%)	58 (8.0%)	53 (7.3%)		81 (13.4%)	70 (11.6%)		69 (25.7%)	60 (22.4%)	
History of congestive heart failure	475 (23.4%)	223 (30.6%)	221 (30.3%)	0.91	121 (20.0%)	112 (18.5%)	0.51	27 (10.1%)	24 (9.0%)	0.66
Duration of qualifying AF ≥2 days	1,406 (69.4%)	519 (71.2%)	525 (72.1%)	0.7	410 (67.7%)	406 (67.0%)	0.81	175 (65.3%)	172 (64.2%)	0.79
First episode of AF (vs. recurrent episode)*	700 (35.8%)	260 (36.6%)	254 (34.8%)	0.48	223 (37.9%)	214 (35.3%)	0.35	78 (29.7%)	73 (27.2%)	0.54
Any pre-randomization failure of an antiarrhythmic drug	364 (18.0%)	146 (20.0%)	139 (19.1%)	0.64	83 (13.7%)	70 (11.6%)	0.26	60 (22.4%)	69 (25.7%)	0.36
Size of left atrium normal†	549 (35.3%)	196 (36.6%)	184 (33.5%)	0.28	175 (36.1%)	172 (35.9%)	0.96	94 (43.1%)	90 (41.9%)	0.79
LVEF†	54.9 ± 13.1	49.4 ± 14.8	48.7 ± 16.9	0.71	57.4 ± 12.1	56.7 ± 11.0	0.64	58.5 ± 11.6	61.4 ± 8.4	0.08
Normal LVEF†	1,131 (74.9%)	326 (63.8%)	324 (61.6%)	0.46	374 (80.1%)	370 (79.4%)	0.8	190 (89.6%)	195 (89.9%)	0.94
Baseline CCS class										
No angina	1,835 (90.5%)	637 (87.4%)	636 (87.2%)	0.98	558 (92.1%)	539 (88.9%)	0.12	256 (95.5%)	258 (96.3%)	0.9
Class I	135 (6.7%)	60 (8.2%)	62 (8.5%)		37 (6.1%)	56 (9.2%)		8 (3.0%)	7 (2.6%)	
Class II or greater	57 (2.8%)	32 (4.4%)	31 (4.3%)		11 (1.8%)	11 (1.8%)		4 (1.5%)	3 (1.1%)	
Baseline NYHA functional class										
No CHF	1,618 (79.8%)	541 (74.2%)	532 (73.0%)	0.10	517 (85.3%)	526 (86.8%)	0.86	242 (90.3%)	240 (89.6%)	0.85
Class I	215 (10.6%)	81 (11.1%)	96 (13.2%)		76 (12.5%)	70 (11.6%)		16 (6.0%)	19 (7.1%)	
Class II	158 (7.8%)	89 (12.2%)	71 (9.7%)		12 (2.0%)	9 (1.5%)		10 (3.7%)	9 (3.4%)	
Class III	36 (1.8%)	18 (2.5%)	30 (4.1%)		1 (0.2%)	1 (0.2%)		0 (0.0%)	0 (0.0%)	

Values are mean ± SD or n (%). Baseline patient characteristics for entire Rate cohort in AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) trial (Overall Rate) and the 3 paired propensity (PS) matched cohorts for individual antiarrhythmic drugs and matched rate control groups. The size of the left atrium was unknown in 185 of 3,311 cases, and left ventricular function (where normal was defined as left ventricular ejection fraction [LVEF] = 0.50) was unknown in 279 of 3,311. Electrocardiogram information was not used in PS models. *This information was not collected on the initial version of the data form and therefore was imputed for 143 patients. †Electrocardiograms were obtained in 3,311 of 4,060.

CHF = congestive heart failure; MI = myocardial infarction; other abbreviations as in Table 1.

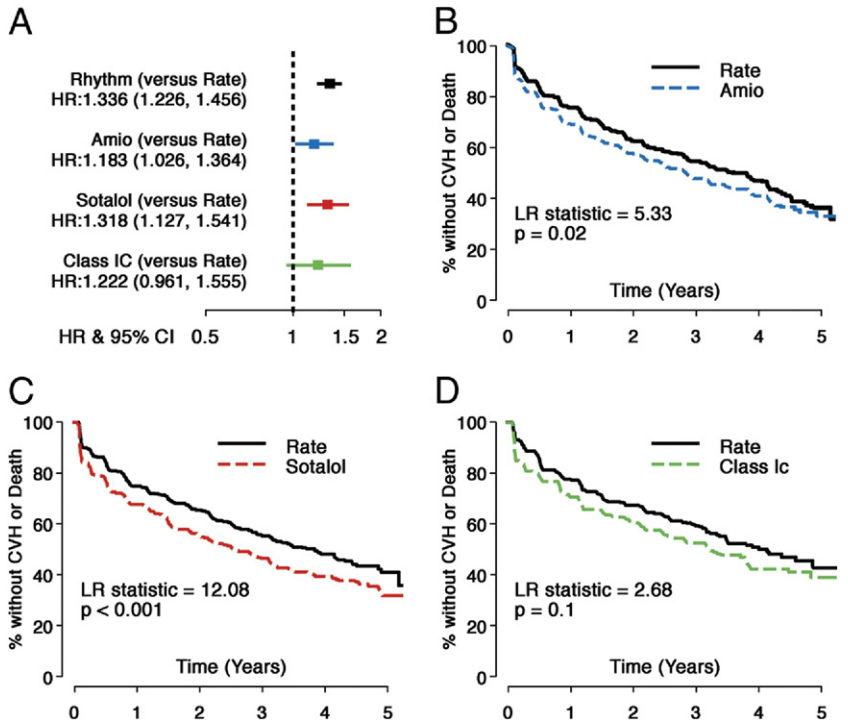

Figure 1 **Comparison of Composite Principal Outcome: Individual AADs Versus Rate**

Hazard ratios (HRs) and Kaplan-Meier survival analyses comparing individual antiarrhythmic drugs (AADs) with matched rate control strategy arm (Rate) cohorts for the composite principal outcome (time to first cardiovascular hospital stay [CVH] or death). Individual panels are shown as follows: **(A)** HRs and 95% confidence intervals (CIs) (HR: rhythm drug/Rate); **(B)** propensity score matched Rate and amiodarone (Amio) subgroups; **(C)** propensity score matched Rate and sotalol subgroups; and **(D)** propensity score matched Rate and Class 1C subgroups. All AADs and matched Rate cohorts show substantial event rates for the principal outcome during follow-up, but all AADs studied had a higher risk of events during follow-up. LR = log rank.

patients but in none of the subgroups examined for the Class 1C patients. These results are detailed in the next section.

CVH categorized by intensity, duration, and associated procedures are tabulated in Table 3. There were substantially more hospital stays of <3-day duration associated with cardioversion in the amiodarone and sotalol cohorts than matched rate cohorts. Cardioversion occurred at similar rates in the matched Class 1C and Rate cohorts (7.2%). Cardiovascular hospital stays with a length of stay of <3 days with a cardioversion procedure alone (without another CV procedure, emergency room visits, or ICU stay [i.e., events that might reflect adherence to AF rhythm control treatment strategy only]) constituted 6.1%, 6.1%, and 4.0% of first CVH for amiodarone, sotalol, and Class 1C, respectively. The corresponding rates in the matched Rate cohorts were 1.9%, 1.6%, and 0.9%, respectively. Stroke, embolism, and major bleeds accounted for only a minority of first CVH in both AAD and rate cohorts (Table 3). Warfarin use at first CVH or death was slightly but not significantly higher in the rate cohorts.

Potential risk factors for CVH. Baseline historical characteristics that increased risk of CVH with AAD, compared with matched Rate cohorts, are shown in Table 4. Female sex was associated with increased risk in sotalol and Class 1C cohorts, compared with matched Rate cohorts, but this was not observed in the amiodarone-Rate cohort comparison. A history of heart failure, coronary disease, and diabetes at enrollment were associated with increased risk for CVH in all AAD cohorts. Pulmonary disease at baseline was associated with increased risk of CVH with amiodarone, and age >75 years was associated with increased risk of CVH with sotalol. There was evidence of significant AAD–comorbidity interactions only in the amiodarone cohort; age >75 years and thyroid disease were associated with increased risk for amiodarone patients but not for their matched Rate counterparts. A significant increased risk for CVH was maintained for amiodarone and sotalol, compared with Rate, despite adjustments for age, sex, or any of these comorbidities.

Time-dependent changes in clinical status that increased risk of CVH are shown in Table 5. In the amiodarone patient cohort, relapse from sinus rhythm to AF and increase in New York Heart Association (NYHA) functional class by 1 or more were associated with a 1.9- and 1.7-fold increase in CVH risk, respectively. For sotalol, relapse from sinus rhythm to AF, increase ≥1 in NYHA functional class, increase in angina class by 1 or more, and ventricular rate increase ≥15 beats/min were all associated

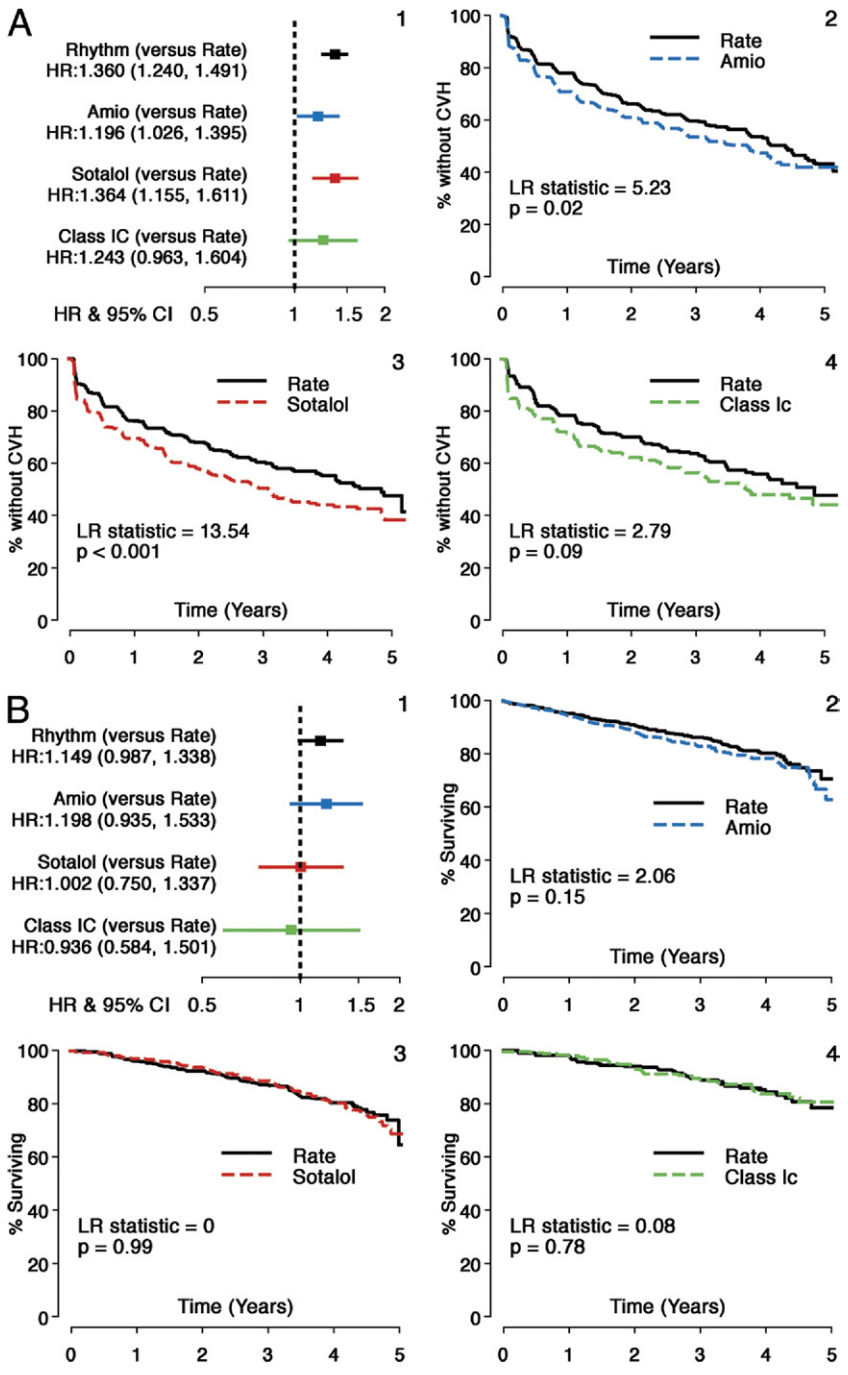

Figure 2 **Components of Principal Outcome—First CVH and Mortality: Individual AADs Versus Rate**

(A) First CVH: individual AADs versus Rate. The HRs and Kaplan-Meier survival analyses comparing individual AADs with matched Rate cohorts for a component of principal outcome: time to first CVH. Individual panels are shown as follows: 1) HRs and 95% CIs (HR: rhythm drug/Rate); 2) propensity score matched Rate and Amio subgroups; 3) propensity score matched Rate and sotalol subgroups; 4) propensity score matched Rate and Class 1C subgroups. All AADs and matched Rate cohorts show substantial event rates during follow-up, but all AADs studied had a significantly higher risk of a first CVH during follow-up. **(B)** Mortality: individual AADs versus Rate. The HRs and Kaplan-Meier survival analyses comparing individual AADs with matched Rate cohorts for a component of principal outcome: time to death. Individual panels are shown as follows: 1) HRs and 95% CIs (HR: rhythm drug/Rate); 2) propensity score matched Rate and Amio subgroups; 3) propensity score matched Rate and sotalol subgroups; and 4) propensity score matched Rate and Class 1C subgroups. Sotalol and Class 1C groups and matched rate cohorts show comparable event rates for risk of death during follow-up, but there is a nonsignificant increase in mortality with Amio compared with its matched Rate cohort. Abbreviations as in Figure 1.

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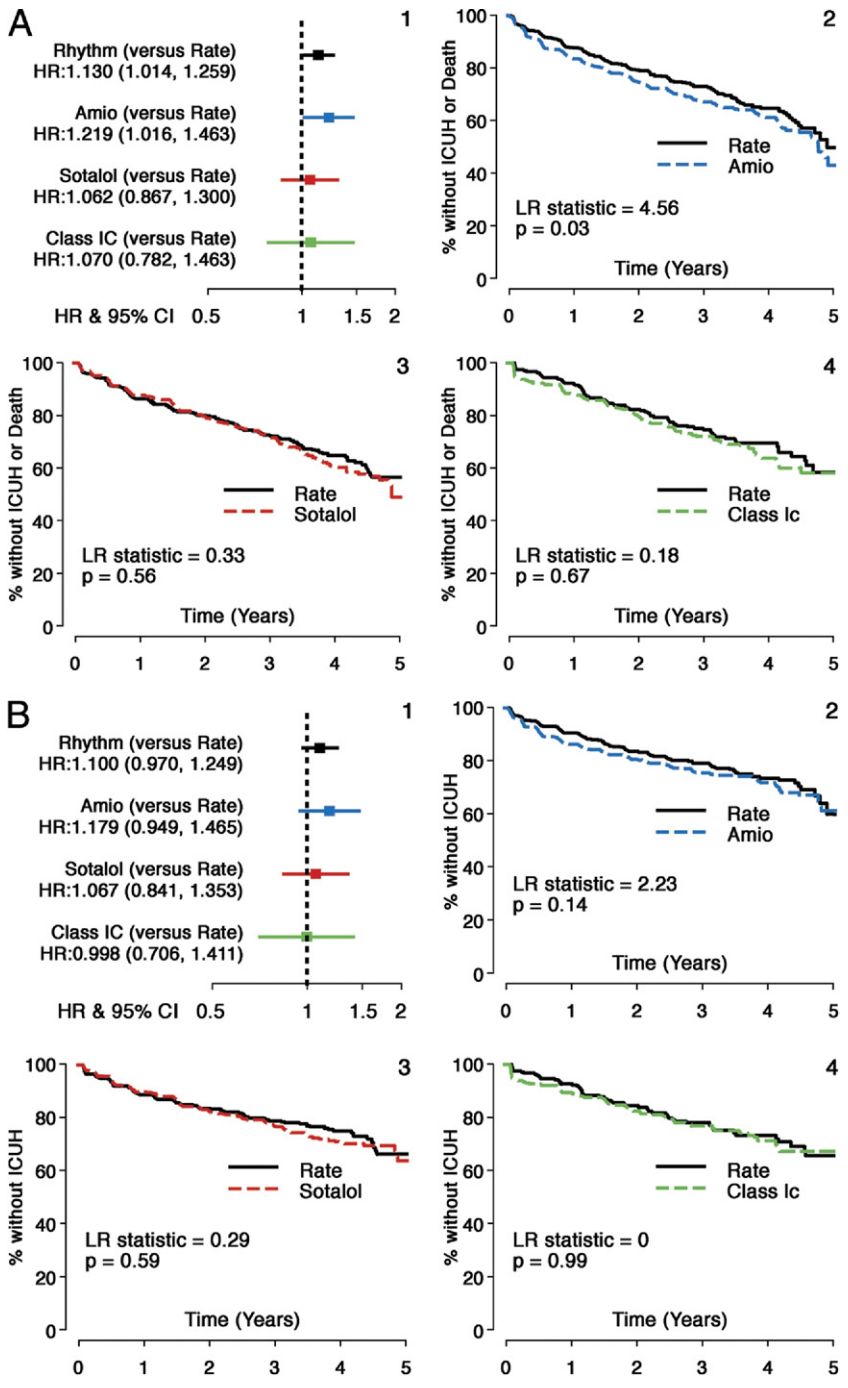

Figure 3 **Comparison of Secondary Composite Outcome—ICUH or Death: Individual AADs Versus Rate**

(A) Secondary composite outcome (intensive care unit hospital stays [ICUH] or death): individual AADs versus Rate. The HRs and Kaplan-Meier survival analyses comparing individual AADs with matched rate cohorts for secondary composite outcome: time to first ICUH or death. Individual panels are shown as follows: 1) HRs and 95% CIs (HR: rhythm drug/Rate); 2) propensity score matched Rate and Amio subgroups; 3) propensity score matched Rate and sotalol subgroups; 4) propensity score matched Rate and Class 1C subgroups. Composite outcome shows that time to ICUH or death was shorter with Amio but not with sotalol or Class 1C versus Rate during follow-up. **(B)** Comparison of ICUH: individual AADs versus Rate. The HRs and Kaplan-Meier survival analyses comparing individual AADs with matched rate cohorts for secondary outcome: time to first ICUH. Individual panels are shown as follows: 1) HRs and 95% CIs (HR: rhythm drug/Rate); 2) propensity score matched Rate and Amio subgroups; 3) propensity score matched Rate and sotalol subgroups; 4) propensity score matched Rate and Class 1C subgroups. Time to ICUH was comparable for sotalol and Class 1C groups, compared with matched Rate cohorts, but a nonsignificant increased risk was seen with Amio compared with Rate during follow-up.

Table 3 Cardiovascular Hospital Stay Profiles in the Propensity Score-Matched Patient Cohorts for Individual Antiarrhythmic Drugs in the AFFIRM Trial

	Amiodarone	Rate	Sotalol	Rate	Class 1C	Rate
CVH	342	309	310	252	126	111
# fatal first CVH	13 (3.8%)	14 (4.5%)	11 (3.5%)	5 (2.0%)	3 (2.4%)	8 (7.2%)
CVH <3 days	96 (28.1%)	95 (30.7%)	82 (26.5%)	70 (27.8%)	41 (32.5%)	35 (31.5%)
CVH <3 days + CV	40 (11.7%)	11 (3.6%)	35 (11.3%)	9 (3.6%)	12 (9.5%)	8 (7.2%)
CVH <3 days, CV, no ER/ICU	21 (6.1%)	6 (1.9%)	19 (6.1%)	4 (1.6%)	5 (4.0%)	1 (0.9%)
CVH >3 days	246 (71.9%)	214 (69.3%)	228 (73.5%)	182 (72.2%)	85 (67.5%)	76 (68.5%)
ICU days first CVH	95 (27.8%)	84 (27.2%)	66 (21.3%)	72 (28.6%)	32 (25.4%)	34 (30.6%)
Warfarin use at first CVH (% of CVH)	279 (81.6%)	275 (89.0%)	273 (88.1%)	227 (90.1%)	108 (85.7%)	101 (91.0%)
Bleeds/stroke/embolic events (% of CVH)	42 (12.3%)	54 (17.5%)	28 (9.0%)	40 (15.9%)	18 (14.3%)	18 (16.2%)
Warfarin use at above event (% of event)	31 (73.8%)	47 (87.0%)	17 (60.7%)	31 (77.5%)	12 (66.7%)	7 (38.9%)

Values are n or n (%).
AFFIRM = Atrial Fibrillation Follow-Up Investigation of Rhythm Management; CV = cardiovascular event; CVH = cardiovascular hospital stay(s); ER = emergency room visit; ICU = intensive care unit stay.

with increased risk for CVH. For Class 1C, ventricular rate increase ≥15 beats/min was associated with increased risk. Higher absolute ventricular rate (in steps of 15 beats/min) was associated with increased risk for sotalol and Class 1C patients. Overall, a higher NYHA functional class was associated with increased risk for all cohorts and higher angina class for amiodarone and Class 1C patients.

Discussion

Analyses of overall and secondary outcomes for the AF population in the AFFIRM study have suggested no overarching benefit of a particular strategy (5,11–13). There was, however, a nonsignificant increase in mortality in the rhythm arm with an excess in pulmonary and cancer deaths (5,14). This finding raised the specter of AAD therapy-related mortality risk. The impact of individual AAD selection on both mortality and hospital stay, compared with Rate, has not been available due to the investigator-determined process for AAD selection, which makes unbiased comparisons challenging. However, such an analysis is still relevant and potentially informative, because most of these agents are currently in widespread clinical use and still employed in clinical trials (15,16).

To evaluate these agents individually, we employed propensity score matching to permit comparative analysis with the rate control patients (17). In this report, it produced highly comparable Rate and AAD cohorts for demographic data, disease status and severity, prior interventions, and therapy (Table 1).

Major Findings of the Study

Clinical outcomes, especially CVH, are affected by initial AAD selection. The present analysis demonstrates inferior performance in the principal clinical outcome for the individual AADs studied versus rate control for the AFFIRM population. This difference in composite outcome was largely due to excess and earlier CVH for each AAD. Sotalol and Class 1C cohorts were comparable to Rate for all-cause mortality. The HR comparing amiodarone with Rate was very similar to the overall AFFIRM study result for mortality risk with rhythm control, but in this small matched cohort the power to see a significant difference was low (<30%). Initial amiodarone therapy was associated with significantly increased risk of non-CV death and mortality plus ICU hospital stay. The sotalol and Class 1C cohorts were similar to Rate with respect to these outcomes,

Table 4 Relationship Between Baseline Characteristics and Risk of CVH

	Amiodarone-Rate Cohort	Sotalol-Rate Cohort	Class 1C-Rate Cohort
Baseline variable			
Heart failure	1.63 (1.4–1.91)*	1.55 (1.29–1.86)*	1.5 (1.08–2.08)†
Female	1.08 (0.92–1.27)	1.23 (1.04–1.46)†	1.37 (1.06–1.78)†
Coronary artery disease	1.83 (1.57–2.14)*	1.4 (1.18–1.65)*	1.37 (1.01–1.85)†
Pulmonary disease	1.3 (1.08–1.58)‡	1.07 (0.82–1.4)	1.23 (0.86–1.74)
Diabetes	1.62 (1.36–1.92)*	1.29 (1.07–1.57)‡	1.56 (1.13–2.15)‡
Thyroid disease	1.44 (1.16–1.79)‡	1.12 (0.88–1.43)	1.26 (0.92–1.73)
Age >75 yrs	1.14 (0.97–1.35)	1.25 (1.05–1.5)†	1.1 (0.81–1.49)
Interactions with treatment			
Rate control × age >75 yrs	0.93 (0.72–1.21)		
Amiodarone × age >75 yrs	1.35 (1.08–1.69)		
Rate × thyroid disease	1.10 (0.80–1.51)		
Amiodarone × thyroid disease	1.92 (1.43–2.59)		

Values are hazard ratio (95% confidence interval). *$p < 0.001$; †$p < 0.05$; ‡$p < 0.01$.

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Table 5 Relationship Between Time Dependent Changes in Clinical Status and Risk of CVH

	Amiodarone vs. Rate	p Value	Sotalol vs. Rate	p Value	Class 1C vs. Rate	p Value
SR to AF	1.87 (1.40–2.50)	<0.0001	1.76 (1.29–2.41)	<0.001	1.11 (0.64–1.94)	0.71
NYHA functional class						
I	1.82 (1.45–2.29)	<0.0001	1.35 (1.00–1.82)	<0.0001	2.17 (1.30–3.63)	<0.0001
II	2.28 (1.78–2.93)		1.81 (1.19–2.77)		1.95 (1.00–3.82)	
III	3.51 (2.42–5.09)		3.72 (2.19–6.33)		4.23 (1.49–12.04)	
IV	7.44 (3.42–16.20)		15.61 (4.65–52.47)		22.45 (6.01–83.82)	
Increase in NYHA functional class	1.72 (1.35–2.20)	<0.0001	1.98 (1.39–2.83)	<0.001	1.25 (0.67–2.34)	0.48
CHC						
I	2.20 (1.68–2.89)	<0.0001	1.26 (0.82–1.92)	0.49	2.58 (1.28–5.19)	<0.001
II	3.57 (2.40–5.30)		1.62 (0.87–3.01)		5.42 (2.09–14.01)	
III	3.73 (1.61–8.64)		2.20 (0.64–7.48)		6.37 (1.19–34.01)	
IV	4.08 (1.29–12.88)		1.96 (0.45–8.61)		28.74 (3.10–266.46)	
Increase in CHC	1.25 (0.87–1.80)	0.22	2.35 (1.40–3.92)	<0.01	0.90 (0.36–2.22)	0.81
VR/15 beats/min	1.13 (1.04–1.24)	<0.01	1.10 (1.00–1.21)	0.05	0.99 (0.84–1.16)	0.9
Increase in VR by ≥15 beats/min	1.25 (0.96–1.64)	0.1	1.58 (1.20–2.07)	<0.01	1.62 (1.04–2.51)	0.03

Values are hazard ratio (HR) (95% confidence interval). HR for ventricular rate (VR) is the increase in risk associated with a 15-beat/min increase in VR.
CHC = Canadian Heart Association classification for angina pectoris; CVH = cardiovascular hospital stay; Sota = sotalol; SR = sinus rhythm; other abbreviations as in Table 1.

suggesting that the excess CVH seen with these drugs were less serious events than those seen with amiodarone.

CVH was extremely common with AF therapies in the AFFIRM trial. From our data, we can estimate overall CVH risk for AF populations and its relation to therapy selection during the period 1995 to 2001. Cardiovascular hospital stay incidence ranged from 36% to 50% at 3 years for rate and rhythm therapies. Cardiovascular hospital stay rates in the AFFIRM Rate subgroups were similar to those seen in the placebo (rate control therapies only) arm of the ATHENA (A placebo-controlled, double-blind, parallel-arm Trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter) trial (36.3% at 2.5 years) (15).

Clinical characteristics and initial AAD selection rather than treatment strategy influenced CVH risk. Potential mechanisms proposed for increased CVH include hospital stays related to change in AAD therapy with associated cardioversion or possible higher warfarin discontinuation rates with potential complications (5,12). Our analysis of CVH related solely to cardioversions for the rhythm control strategy, although higher than in matched Rate cohorts, demonstrated a fairly low incidence in all AAD cohorts. Stoke, embolism, and major bleeds also had a low incidence that was comparable in the matched Rate cohorts. Longer hospital stays, ICU stays, and other CV procedures constituted the bulk of CVH, suggesting more serious clinical conditions. Differences in CVH rates persisted across clinically important subgroups, such as elderly persons, women, and coronary disease patients.

CVH in AF: insights from the AFFIRM trial. CVH has become a major endpoint for clinical trials. It can impact treatment strategy recommendations and regulatory approval of new therapies but is rarely used in AF trials (15,18–20). CVH in AF are costly, with average costs estimated to exceed $12,000/AF admission in the United States and $3 billion in annual costs (21). Atrial fibrillation hospital stays are widely assumed to be related to AF recurrences, but such an assumption has neither been critically verified and quantified, nor has the uniformity of this risk been assessed across AF subpopulations or treatments (22).

To date, small trials of nonpharmacologic therapies and 1 large pharmacologic therapy trial have provided some information about CVH in AF (15,18–20). Analysis of the AFFIRM database provides important additional data from a large randomized controlled trial over a long follow-up. CVH presaged mortality, but it was unclear how these events related to treatment strategy and clinical condition (12). Given the observations with respect to ICU hospital stays, CVH are usually related to serious morbidity, with treatment strategy-related hospital stays—such as for a change of drug therapy or for cardioversion—being a relatively small component. Excess CVH events observed with the AADs evaluated are associated with age, sex, and comorbidity status. There is a residual excess CVH risk even after adjustment for these historical factors, which is related to AAD use. Additionally, CVH risk can be related to changes in cardiovascular disease status longitudinally. Time-dependent changes that impact risk can include either AF relapses or worsening of major cardiovascular symptoms of the underlying disease. We propose, on the basis of our analysis, that both baseline patient characteristics and time-dependent changes in clinical status contribute to CVH risk. Any heart failure or coronary disease was associated with increased risk in all 3 matched cohorts but was more common in the amiodarone and matched Rate cohorts. An increase in heart failure or angina class

by 1 or more increased risk of CVH. These findings make a strong case for baseline disease state variables and change in clinical status leading to CVH.

Relapse from sinus rhythm to AF was also related to CVH, suggesting failure of rhythm control as a potential mechanism. Finally, specific interactions of antiarrhythmic agents such as amiodarone with comorbidities such as thyroid disease suggest additional mechanisms leading to hospital stay. The reasons for CVH are multiple and multifactorial. Atrial fibrillation patients have varying risk for the principal outcome in this analysis on the basis of these factors.

Study Limitations

Propensity score matching cannot correct for erroneous omission or inclusion of variables that might have affected AAD selection, but it is a significant improvement over naïve subgroup analyses. Some of the hospital stays might be the result of routine patient care for rhythm control rather than for medical necessity, but these still occur in current clinical practice. The AFFIRM study did not capture detailed reasons for hospital stay or drug doses. Exact dates of hospital stay were not collected, which results in decreased precision in estimates of time to hospital stay but probably not for the comparison of matched cohorts.

Conclusions

CV hospitalizations were common in AFFIRM with both treatment strategies but more frequent with amiodarone, sotalol and class 1C agents. The severity of this risk varied with the individual AAD, patient characteristics and time dependent changes in clinical status, but was largely unrelated to the rhythm treatment algorithm. Death, intensive care unit hospital stay, and non-CV death were more frequent with amiodarone.

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Key Words: antiarrhythmic drugs ■ atrial fibrillation ■ cardiovascular hospitalizations ■ cardiovascular outcomes ■ clinical trials ■ outcomes research.

APPENDIX

For list of investigators and affiliated institutions, please see the online version of this article.